Amendment to the Claims:

Please amend the claims as follows.

Please cancel claims 32, 44, 45, 52 to 54, 56, 57, 63, 64, without prejudice or disclaimer.

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

Claim 1 (currently amended): A method for producing a recombinant antibody or antigen binding fragment thereof with improved yield from a host cell, comprising:

(i) providing a nucleic acid encoding a ~~modified~~ non-human antibody or antigen binding fragment thereof made by a method comprising:

(a) aligning a hypervariable region (HVR1) and/or a hypervariable region 2 (HVR2) of a variable domain of a non-human antibody or antigen binding fragment thereof to corresponding HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences;

(b) selecting a human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the non-human HVR1 sequence and/or the non-human HVR2 sequence;

(c) identifying at least one amino acid position in at least one framework region (FR) of the selected human subgroup variable domain consensus sequence that has a different amino acid residue than that of a corresponding position in a FR of the variable domain of the non-human antibody or antigen binding fragment thereof; and

(d) substituting at least ~~modifying~~ one amino acid at the corresponding position of the non-human variable domain of the antibody or antigen binding fragment thereof to be the same as the different human amino acid residue identified in (c) to form a substituted ~~modified~~ FR ~~region~~ in the non-human variable domain of the antibody or antigen binding fragment thereof; and

(ii) expressing the substituted ~~modified~~ non-human antibody or antigen binding fragment thereof in the host cell,

wherein the substituted ~~modified~~ non-human antibody or antigen binding fragment thereof having the at least one substitution has improved yield in a cell or a cell culture as compared to the corresponding unsubstituted ~~unmodified~~ antibody or antigen binding fragment thereof.

Claim 2 (currently amended): The method according to claim 1, wherein the non-human antibody or antigen binding fragment thereof to be substituted ~~modified~~ is selected from the group consisting of a humanized antibody, a chimeric antibody, a monoclonal antibody, a multispecific antibody, a diabody, or an antibody generated by phage display.

Claim 3 (currently amended): The method according to claim 2, wherein the non-human antigen binding fragment thereof is a Fab fragment, $F(ab')_2$ fragment, scFV fragment, or $sc(Fv)_2$ fragment, a single arm antibody or single chain antibody.

Claim 4 (currently amended): The method according to claim 1, wherein the non-human antibody is an anti-vascular endothelial growth factor (VEGF) ~~anti-VEGF~~ antibody.

Claim 5 (previously presented): The method according to claim 4, wherein the non-human antibody is a humanized antibody.

Claim 6 (canceled)

Claim 7 (currently amended): The method of claim 1, wherein the ~~nucleic acid encoding the modified~~ substituted non-human antibody or antigen binding fragment thereof further comprises ~~a nucleic acid encoding~~ a constant region domain, and the constant region domain ~~domain encoding nucleic acid~~ is connected to the antibody or antigen binding fragment thereof ~~fragment encoding nucleic acid~~ to form a ~~nucleic acid encoding a~~ full-length heavy and/or light chain.

Claim 8 (currently amended): The method of claim 1, wherein the ~~host cell comprises an expression vector comprising the~~ nucleic acid encoding the substituted recombinant ~~modified~~ non-human antibody or antigen binding fragment thereof is contained in an expression vector.

Claim 9 (currently amended): The method of claim 7, further comprising recovering a ~~modified~~ substituted non-human full-length heavy or light chain or both from the culture.

Claim 10 (previously presented): The method according to claim 1, wherein the host cell is a prokaryotic host cell.

Claim 11 (previously presented): The method according to claim 1, wherein the host cell is a mammalian cell.

Claim 12 (currently amended): The method according to claim 1, further comprising isolating the expressed non-human heavy chain variable domain having a ~~modified~~ substituted FR ~~region~~ or the ~~modified~~ substituted non-human light chain variable domain having a ~~modified~~ substituted FR ~~region~~.

Claim 13 (currently amended): The method according to claim 12, wherein the non-human variable domain is a heavy chain variable domain and the HVR1 amino acid sequence of the heavy chain variable domain of the antibody or antigen binding fragment thereof is GYTFTNYGIN (SEQ ID NO: 14) or GYDFTHYGMN (SEQ ID NO:18).

Claim 14 (currently amended): The method according to claim 1, wherein the non-human framework region to be ~~modified~~ substituted is selected from the group consisting of a FR1, a FR2, a FR3, a FR4 and a mixture thereof.

Claim 15 (previously presented): The method according to claim 14, wherein the human subgroup variable domain consensus sequence comprises a variable domain FR1 sequence with a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2 and SEQ ID NO:3.

Claim 16 (currently amended): The method according to claim 1, wherein the yield of the non-human antibody or antigen binding fragment thereof comprising the ~~modified~~ substituted FR is improved at least 2 fold compared to the corresponding ~~unmodified~~ unsubstituted antibody or antigen binding fragment thereof.

Claim 17 (currently amended): The method according to claim 16, wherein the yield of the non-human antibody or antigen binding fragment thereof comprising the ~~modified~~ substituted FR is improved at least 2 fold to 16 fold compared to the corresponding ~~unmodified~~ unsubstituted antibody or antigen binding fragment thereof.

Claim 18 (currently amended): The method of claim 1, wherein in step (d) at least two, three, four, five, six or seven amino acid positions in the non-human FR are substituted ~~modified~~.

Claim 19 (currently amended): The method of claim 1, wherein the non-human antibody or antigen binding fragment thereof is an anti-vascular endothelial growth factor (VEGF) ~~a VEGF~~ antibody or antigen binding fragment thereof comprising a heavy chain variable domain FR1 sequence of SEQ ID NO:3, and the FR is a heavy chain variable domain FR1 and one of the amino acid positions is position 6 or position 23 or both, and the other position is selected from the group consisting of position 1, 11, 13, 18, 19, and a mixture thereof.

Claim 20 (currently amended): The method of claim 19, wherein amino acid positions 6 and 23 are substituted ~~modified~~.

Claim 21 (currently amended): The method of claim 19, wherein the amino acid positions at positions 1, 6, 11, 13, 18, 19, and 23 of the heavy chain FR1 are substituted ~~modified~~.

Claim 22 (currently amended): The method of claim 1, wherein at least 95% ~~one but not all~~ of the different amino acid positions in the non-human FR are substituted ~~modified~~.

Claim 23 (currently amended): The method of claim 22, wherein the ~~modified~~ substituted FR is FR1, FR2, or FR3.

Claim 24 (currently amended): The method of claim 1, wherein ~~at least one but not~~ all of the amino acid positions that have a different amino acid as compared to the human consensus sequence in all framework regions (FRs) of the non-human variable region are substituted ~~modified~~.

Claim 25 (currently amended): A method for preparing a humanized antibody or an antigen binding fragment thereof having an improved folding efficiency and yield when expressed in a host cell, comprising:

(a) preparing a humanized antibody or antigen binding fragment thereof comprising a variable domain comprising at least one ~~modified~~ substituted framework region (FR) sequence, wherein the variable domain is made by a method comprising:

(i) aligning a hypervariable region (HVR1) and/or a hypervariable region 2 (HVR2) of a variable domain of a non-human antibody or antigen binding fragment thereof to corresponding HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences;

(ii) selecting a human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the non-human HVR1 sequence and/or the non-human HVR2 sequence;

(iii) identifying at least one amino acid position in at least one framework region (FR) of the human subgroup variable domain consensus sequence selected in step (ii) that has a different amino acid residue than that of a corresponding position in a FR of the variable domain or antigen binding fragment thereof of the non-human antibody; and

(iv) substituting ~~modifying~~ one amino acid at the corresponding position of the non-human variable domain or antigen binding fragment thereof of the antibody to be the same as the different human amino acid residue identified in **(iii)** **[[**(c)**]]** to form a ~~modified~~ substituted FR ~~region~~ in the non-human variable domain or antigen binding fragment thereof of the antibody,

wherein the substitution ~~modification~~ results in an antibody or antigen binding fragment thereof having an improved folding efficiency and yield when expressed in the host cell, and

(b) expressing the ~~modified~~ substituted humanized antibody or ~~modified~~ substituted antigen binding fragment thereof in the host cell.

Claims 26 to 27 (canceled)

Claim 28 (currently amended): The method according to claim 25 wherein the non-human variable domain is a heavy chain variable domain and the HVR1 amino acid sequence of a heavy chain variable domain of the non-human antibody or antigen binding fragment thereof is GYTFTNYGIN (SEQ ID NO: 14) or GYDFTHYGMN (SEQ ID NO:18).

Claim 29 (previously presented): The method according to claim 25, wherein the FR is selected from the group consisting of a FR1, a FR2, a FR3, a FR4 and a mixture thereof.

Claim 30 (previously presented): The method according to claim 29, wherein the human subgroup variable domain consensus sequence comprises a heavy chain variable domain FR1 sequence with a sequence selected from the group consisting of SEQ. ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3.

Claim 31 (currently amended): The method of claim 25, wherein ~~at least one but not~~ all of the different amino acid positions in the non-human FR are ~~modified~~ substituted.

Claim 32 (canceled)

Claim 33 (currently amended): The method of claim 25, wherein the ~~host cell comprises an expression vector comprising the~~ nucleic acid encoding the substituted recombinant ~~modified~~ non-human antibody or antigen binding fragment thereof is contained in an expression vector.

Claim 34 (currently amended): The method of claim 25 **[[**33**]]**, wherein the nucleic acid further comprises a sequence encoding a constant domain connected to the ~~nucleic acid encoding the modified~~ substituted non-human antibody or antigen binding fragment thereof to form a ~~nucleic acid encoding a~~ full-length heavy or light chain.

Claim 35 (canceled)

Claim 36 (previously presented): The method according claim 25, wherein the host cell is a prokaryotic host cell.

Claim 37 (previously presented): The method according to claim 25, wherein the host cell is a mammalian cell.

Claim 38 (currently amended): A method for improving the yield of an assembled non-human monoclonal antibody or antigen binding fragment thereof in a host cell, comprising:

(a) aligning a hypervariable region 1 (HVR1) and/or a hypervariable 2 (HVR2) sequence of a heavy chain variable domain of the non-human monoclonal antibody to corresponding HVR1 and/or HVR2 sequences of human subgroup heavy chain variable domain consensus sequences,

(b) selecting a human subgroup heavy chain variable domain consensus sequence that has the HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the HVR1 and/or the HVR2 sequence of the heavy chain variable domain of the non human monoclonal antibody,

(c) substituting ~~modifying~~ at least one ~~but not all~~ amino acid position ~~positions~~ in at least one framework region (FR) of the non-human monoclonal antibody heavy chain variable domain for **[[**to**]]** an amino acid residue found at a corresponding position of the selected human subgroup heavy chain variable domain consensus sequence to form at least one ~~modified~~ substituted FR, wherein the non-human monoclonal antibody or antigen binding fragment thereof with the ~~modified~~ substituted FR has improved folding efficiency and yield, in cell culture compared to the folding efficiency and yield of a corresponding ~~unmodified~~ unsubstituted antibody or antigen binding fragment thereof; and

(d) expressing the non-human monoclonal antibody or antigen binding fragment thereof comprising the ~~modified~~ substituted FR in the host cell.

Claim 39 (currently amended): A method for improving the yield of a recombinant antibody or antigen binding fragment thereof expressed in a host cell, comprising:

(a) selecting a human subgroup variable domain consensus sequence by aligning a hypervariable region 1 (HVR1) and/or a hypervariable 2 (HVR2) sequence of a variable domain of a non-human antibody or antigen binding fragment thereof to corresponding HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences, and selecting the human subgroup variable domain consensus sequence that has the HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the HVR1 and/or HVR2 sequence of the variable domain of the non-human antibody or antigen binding fragment thereof, and

(b) substituting ~~modifying~~ at least one ~~but not all~~ amino acid residue ~~residues~~ in the framework region (FR) of the variable domain of the non-human antibody or antigen binding fragment thereof to an amino acid at the corresponding position in ~~such that the modified FR has at least 50% sequence identity to the corresponding FR amino acid sequence of~~ the selected human subgroup variable domain consensus sequence to form a modified FR,

wherein the amino acid residues in the FR ~~framework (FR)~~ are ~~modified~~ substituted to the amino acid residue **at [[**of**]]** the corresponding human subgroup variable domain consensus sequence amino acid,

wherein **[[**and**]]** the recombinant antibody or antigen binding fragment thereof with the ~~modified~~ substituted FR has improved folding efficiency and yield **[[**,**]]** in cell culture compared to the folding efficiency and yield of a corresponding ~~unmodified~~ unsubstituted antibody or antigen binding fragment thereof;

(c) expressing the recombinant antibody or antigen binding fragment thereof with the ~~modified~~ substituted FR in the host cell and recovering the antibody or antigen binding fragment thereof with the ~~modified~~ substituted FR from the host cell.

Claim 40 (currently amended): The method according to claim 39, wherein the variable domain is a heavy chain variable domain and the HVR1 amino acid sequence of a heavy chain variable domain of the antibody or antigen binding fragment thereof is GYTFTNYGIN (SEQ ID NO: 14) or GYDFTHYGMN (SEQ ID NO: 18).

Claim 41 (currently amended): The method of claim 39, wherein at least two ~~but not all~~ amino acid positions that have a different amino acid in at least one FR are substituted with amino acids in the corresponding position of the selected human subgroup consensus sequence.

Claim 42 (currently amended): The method of claim 41, wherein the antibody or antibody binding fragment thereof is an anti-vascular endothelial growth factor (VEGF) ~~a VEGF~~ antibody or antibody binding fragment thereof comprising a heavy chain variable domain FR1 comprising the amino acid sequence of SEQ ID NO:3 and amino acid positions 6 and 23 of heavy chain FR1 are ~~modified~~ substituted.

Claim 43 (currently amended): The method of claim 42, wherein amino acid positions 1, 6, 11, 13, 18, 19 and 23 of the heavy chain FR1 are ~~modified~~ substituted.

Claims 44 to 45 (canceled)

Claim 46 (previously presented): The method according to claim 38, wherein the host cell is a prokaryotic host cell.

Claim 47 (previously presented): The method according to claim 38, wherein the host cell is a mammalian cell.

Claim 48 (currently amended): The method according to claim 39, wherein the step of **(b)** comprises substituting at least ~~modifying~~ one ~~but not all~~ amino acid residue ~~residues~~ in all of the FRs of the variable domain with amino acid residues **at [[**of**]]** the corresponding human subgroup variable domain consensus sequence.

Claim 49 (previously presented): The method according to claim 38, wherein the framework region sequence is selected from the group consisting of FR1, FR2, FR3, FR4 and a mixture thereof.

Claim 50 (currently amended): A method for producing **[[**an**]]** a vascular endothelial growth factor (VEGF) antibody or an antigen binding fragment thereof expressed with improved yield from a host cell comprising:

(a) aligning a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) sequence of a non-human monoclonal antibody to corresponding HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences,

(b) selecting a human subgroup variable domain consensus sequence that has the HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the HVR1 and/or HVR2 sequence of the non human monoclonal antibody,

(c) identifying at least one amino acid position proximal to a cysteine (cys) residue that participates in an intrachain variable domain disulfide bond in the selected human subgroup variable domain consensus sequence in step (b) having a different amino acid than that found at a corresponding position of the non-human antibody or antigen binding fragment's variable domain,

(d) substituting at least one ~~modifying~~ the amino acid at the corresponding position of the non-human antibody or antigen binding fragment thereof with the different amino acid of the

selected human subgroup variable domain consensus sequence to form a ~~modified~~ substituted variable domain; and

(e) expressing the recombinant antibody or antigen binding fragment thereof comprising the ~~modified~~ substituted variable domain in the host cell,

wherein the ~~modified~~ substituted recombinant antibody or antigen binding fragment thereof has improved folding efficiency and yield, in cell culture as compared to the folding efficiency and yield of an ~~unmodified~~ unsubstituted antibody or antigen binding fragment thereof.

Claim 51 (currently amended): The method according to claim 50, wherein the variable domain of the non-human antibody is a heavy chain variable domain or a light chain variable domain.

Claims 52 to 54 (canceled)

Claim 55 (previously presented): The method according to claim 50, wherein the one amino acid position is an amino acid position adjacent to the cysteine (cys) residue that forms an intra chain variable domain disulfide bond.

Claims 56 to 57 (canceled)

Claim 58 (previously presented): The method according to claim 50, wherein the non-human variable domain is from an anti-VEGF antibody.

Claim 59 (currently amended): The method according to claim 50, wherein the non-human variable domain is from a humanized antibody or antigen binding fragment thereof.

Claim 60 (currently amended): The method according to claim 50, wherein the ~~host cell comprises an expression vector comprising a~~ nucleic acid encoding the ~~modified~~ substituted recombinant variable domain is contained in an expression vector.

Claim 61 (currently amended): The method according to claim 60, wherein: (a) the expression vector further comprises a second nucleic acid encoding an antibody constant region domain, (b) the nucleic acid encoding the ~~modified~~ substituted variable domain and the second nucleic acid are operably linked to a promoter; (c) the method of (a) or (b), wherein the nucleic acid further comprises a heat stable enterotoxin sequence that can direct secretion to a host cell periplasm; or (d) the method of any of (a) to (c), wherein the nucleic acid further comprises a terminator sequence.

Claim 62 to 64 (canceled)

Claim 65 (previously presented): The method according to claim 50, wherein the host cell is a prokaryotic host cell.

Claim 66 (previously presented): The method according to claim 50, wherein the host cell is a eukaryotic host cell.

Claim 67 (currently amended): The method according to claim 50, wherein the expressed recombinant antibody or antigen binding fragment thereof with ~~modified~~ a substituted variable domain has increased yield of at least 2 fold when produced in cell culture as compared to the ~~unmodified~~ unsubstituted antibody or antigen binding fragment thereof.

Claim 68 (currently amended): The method according to claim 67, wherein the yield of the expressed recombinant antibody or antigen binding fragment thereof with the ~~modified~~ substituted variable domain is increased at least 2 to 16 fold as compared to the ~~unmodified~~ unsubstituted antibody or antigen binding fragment thereof.

Claim 69 (currently amended): The method of claim 50 further comprises:

(a) identifying at least one amino acid position in a second variable domain of the non-human antibody or antigen binding fragment thereof that is proximal to a cysteine (cys) residue that participates in an intrachain variable domain disulfide bond in the second variable domain;

(b) selecting a human subgroup variable domain consensus sequence having the most sequence identity with a HVR1 and/or HVR2 amino acid sequence of the second non-human variable domain; and

(c) determining whether the amino acid in the amino acid position identified in the second non-human variable domain is different than the amino acid in the selected human subgroup variable domain consensus sequence; and

(d) placing at the at least one position in the second non-human variable domain the different amino acid found at the corresponding position in the selected human subgroup variable domain consensus sequence to form a ~~modified~~ substituted variable domain.

Claim 70 (previously presented): The method of claim 69, wherein the non-human variable domain is a heavy chain variable domain and the second non-human variable domain is a light chain variable domain.

Claim 71 (currently amended): A method for preparing a recombinant humanized non-human monoclonal antibody or antigen binding fragment thereof, comprising:

(a) substituting ~~modifying~~ at least one amino acid position proximal to a cysteine (cys) residue that participates in an intrachain variable domain disulfide bond in a non-human variable domain with a different amino acid, wherein the different amino acid is determined by aligning the a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) sequence of a non-human monoclonal antibody to corresponding HVR1 and/or HVR2 sequences of human subgroup consensus sequences, and selecting the amino acid found at the corresponding position of the human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the HVR1 and/or HVR2 amino acid sequence of the non-

human monoclonal antibody as the different amino acid to form a ~~modified~~ substituted variable domain;

(b) expressing a recombinant humanized antibody or antigen binding fragment thereof comprising the ~~modified~~ substituted variable domain in a host cell; and

(c) recovering the ~~modified~~ substituted recombinant humanized antibody or antigen binding fragment thereof from the host cell.

Claim 72 (previously presented): The method according to claim 71, wherein the non-human variable domain is a heavy chain variable domain.

Claim 73 (previously presented): The method according to claim 71, wherein the non-human variable domain is a light chain variable domain.

Claim 74 (currently amended): A method for improving the yield of an antibody or fragment thereof, comprising:

(a) identifying at least one amino acid position in a non-human heavy chain variable domain that is proximal to a cysteine (cys) residue that participates in an intrachain disulfide bond in the heavy chain variable domain;

(b) aligning a hypervariable 1 (HVR1) and/or hypervariable region 2 (HVR2) of the non-human heavy chain variable domain of step a) to corresponding HVR1and/or HVR2 sequences of human subgroup heavy chain variable domain consensus sequences;

(c) selecting a human subgroup heavy chain variable domain consensus sequence having the most identity with the HVR1 and/or HVR2 amino acid sequence of the non-human heavy chain variable domain; and

(d) substituting ~~modifying~~ the selected position in the non-human heavy chain variable domain an amino acid with the corresponding position in the selected human subgroup heavy chain variable domain consensus sequence to form a ~~modified~~ substituted non-human heavy chain variable domain;

(e) identifying at least one amino acid position in a non-human light chain variable domain that is proximal to a cysteine (cys) residue that participates in an intrachain disulfide bond in the light chain variable domain;

(f) aligning a HVR1 and/or HVR2 of the light chain variable domain of step e) to corresponding HVR1 and/or HVR2 sequences of human subgroup light chain variable domain consensus sequences;

(g) selecting a human subgroup light chain variable domain consensus sequence having the most sequence identity with the HVR1 and/or HVR2 amino acid sequence of the non-human light chain variable domain;

(h) substituting ~~modifying~~ the selected position in the non-human light chain variable domain an amino acid with the corresponding position in the selected human subgroup light chain variable domain consensus sequence to form a ~~modified~~ substituted non-human light chain variable domain; and

(i) expressing the recombinant antibody or antigen binding antibody fragment thereof comprising the ~~modified~~ substituted non-human heavy chain variable domain and the ~~modified~~ substituted non-human light chain variable domain in a host cell, wherein the ~~modified~~ substituted antibody or antigen binding antibody fragment thereof has improved folding efficiency and yield in the host cell as compared to the folding efficiency and yield of an ~~unmodified~~ unsubstituted antibody or antigen binding antibody fragment.

Claims 75 to 95 (canceled)

Claim 96 (currently amended): A method for improving the yield of antibody or antigen binding fragment thereof in a host cell or cell culture, comprising:

a) expressing a nucleic acid encoding a variable domain of a non-human antibody or antigen binding fragment thereof comprising at least one ~~modified~~ substituted framework region (FR) in the host cell, wherein the ~~modified~~ substituted FR has: (i) a substitution of at least one ~~but not all~~ amino acids in the at least one FR with a different amino acid, or (ii) a deletion of at least one ~~but not all~~ amino acids in the FR,

wherein the amino acid residue or residues to be substituted or deleted is determined by aligning a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) sequence of the non-human variable domain of the antibody or antigen binding fragment thereof to corresponding HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences, and selecting the amino acid found at the corresponding FR position of the human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the HVR1 and/or HVR2 sequence of the non-human variable domain of the recombinant antibody or antigen binding fragment thereof, and

b) recovering the recombinant antibody or antigen binding fragment thereof comprising the non-human variable domain comprising the ~~modified~~ substituted FR from the host cell, wherein the ~~modified~~ substituted antibody or antigen binding fragment thereof has improved folding efficiency and yield in the cell or cell culture as compared to the folding efficiency and yield of an ~~unmodified~~ unsubstituted antibody or antigen binding fragment thereof.

Claim 97 (previously presented): The method according to claim 96, wherein: (a) the nucleic acid is contained in an expression vector, (b) the nucleic acid is operably linked to a promoter, (c) the method of (a) or (b), wherein the nucleic acid further comprises a heat stable enterotoxin sequence that can direct secretion to the periplasm, or (d) the method of any of (a) to (c), wherein the nucleic acid further comprises a terminator sequence.

Claim 98 (previously presented): The method according to claim 96, wherein the host cell is a prokaryotic host cell.

Claim 99 (previously presented): The method according to claim 96, wherein the host cell is a eukaryotic host cell.

Claim 100 (currently amended): A method for improving the yield of an antibody or antigen binding fragment thereof in a host cell or cell culture, comprising:

(A) expressing a nucleic acid molecule encoding a ~~modified~~ substituted variable domain of a non-human antibody or antigen binding fragment thereof in the host cell or cell culture, wherein the ~~modified~~ substituted variable domain has: (i) a substitution of at least one ~~but not all~~ amino acids proximal to a cysteine (cys) reside that participates in an intrachain variable domain disulfide bond with a different amino acid, or (ii) deleting at least one ~~but not all~~ amino acids proximal to a cys reside that participates in an intrachain variable domain disulfide bond, wherein the substituted or deleted amino acid is determined by:

(a) aligning a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) sequence of the variable domain of the non-human antibody or antigen binding fragment thereof to corresponding HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences, and

(b) selecting the amino acid found at the corresponding position of the human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the HVR1 and/or HVR2 amino acid sequence of the non-human variable domain as the different amino acid, and

(B) recovering the recombinant antibody or antigen binding fragment thereof comprising the ~~modified~~ substituted variable domain from the host cell, wherein the antibody or antigen binding fragment thereof has improved folding efficiency and yield in the host cell or cell culture as compared to the folding efficiency and yield of a **[[**the**]]** corresponding ~~unmodified~~ unsubstituted antibody or antigen binding fragment thereof.

Claim 101 (currently amended): The method according to claim 100, wherein: (a) the host cell comprises an expression vector that comprises the nucleic acid molecule encoding the ~~modified~~ substituted variable domain; (b) the nucleic acid molecule encoding the ~~modified~~ substituted variable domain is operably linked to a promoter, (c) the method of (a) or (b), wherein the nucleic acid further comprises a heat stable enterotoxin sequence that can direct secretion to a periplasm of

the host cell, or (d) the method of any of (a) to (c), wherein the nucleic acid further comprises a terminator sequence.

Claim 102 (previously presented): The method according to claim 100, wherein the host cell is a prokaryotic host cell.

Claim 103 (previously presented): The method according to claim 100, wherein the host cell is a eukaryotic host cell.

Claim 104 (currently amended): A method for improving the yield of a non-human antibody, or antigen binding fragments thereof, in a host cell or cell culture comprising:

(a) comparing a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) amino acid sequence of a heavy chain variable domain of the non-human antibody or antigen binding fragment thereof to a corresponding HVR1 and/or HVR2 amino acid sequence of each human subgroup heavy chain variable domain consensus sequence and selecting the human subgroup heavy chain variable domain consensus sequence that has the most sequence identity with the HVR1 and/or HVR2 sequence of the heavy chain variable domain of the non-human antibody or antigen binding fragment thereof;

(b) identifying at least one amino acid position in at least one framework region (FR) in the heavy chain variable domain of the non-human antibody or antigen binding fragment thereof selected from the group consisting of a FR1, a FR2, a FR3, a FR4 and a mixture thereof, wherein the amino acid position has a different amino acid than the amino acid at a corresponding position of the selected human subgroup heavy chain variable domain consensus sequence; and

(c) substituting ~~modifying~~ or deleting at least one ~~but not all~~ of the amino acid positions identified in step (b), wherein the substitution ~~modification~~ or deletion is with the amino acid in the corresponding position of the selected human heavy chain subgroup variable domain consensus sequence, to form a variable domain with a ~~modified~~ substituted FR; and

(d) expressing the recombinant antibody or antigen binding fragment thereof comprising the heavy chain variable domain with the ~~modified~~ substituted FR in the host cell or cell culture, and

(e) recovering the antibody or antigen binding fragment thereof from the host cell or cell culture,

wherein the recombinant antibody or antigen binding fragment thereof with the ~~modified~~ substituted FR has improved yield in the host cell or cell culture compared to the folding efficiency and yield of a corresponding ~~unmodified~~ unsubstituted non-human antibody or antigen binding fragment thereof.

Claim 105 (previously presented): The method according to claim 104, wherein the non-human antibody is selected from the group consisting of a humanized antibody, a chimeric antibody, a monoclonal antibody, a multispecific antibody, a diabody, or an antibody generated by phage display.

Claim 106 (currently amended): The method according to claim 105, wherein the non-human antigen binding fragment thereof is a Fab fragment, $F(ab')_2$ fragment, scFV fragment, or $sc(Fv)_2$ fragment, single arm antibody, or single chain antibody.

Claim 107 (previously presented): The method according to claim 104, wherein the non-human antibody is an anti-VEGF antibody.

Claim 108 (previously presented): The method according to claim 107, wherein the non-human antibody is a humanized antibody.

Claim 109 (currently amended): The method of claim 104, wherein step (c) comprises substituting ~~modifying~~ a nucleic acid encoding the non-human variable domain to form a nucleic acid encoding a variable domain with a ~~modified~~ substituted FR, wherein the ~~modified~~ substituted FR has at least one ~~but not all~~ of the amino acid positions: (i) substituted with the amino acid in the corresponding position of the selected human subgroup variable domain consensus sequence; or (ii) deleted.

Claim 110 (currently amended): The method of claim 109, wherein the variable domain ~~domain-encoding nucleic acid~~ further comprises a ~~nucleic acid encoding a~~ constant region domain, and the constant region domain ~~domain-encoding nucleic acid~~ is connected to the ~~nucleic acid encoding the~~ variable domain with the ~~modified~~ substituted FR to form a ~~nucleic acid encoding a~~ variant full-length heavy or light chain.

Claim 111 (currently amended): The method of claim 109, wherein the ~~modified~~ substituted nucleic acid is comprised within an expression vector.

Claim 112 (currently amended): The method of claim 111, further comprising culturing a host cell comprising the expression vector or the ~~modified~~ substituted nucleic acid under conditions wherein the recombinant antibody chains are expressed; and recovering a full-length heavy or light chain or both from the cell or cell culture.

Claim 113 (original): The method according to claim 112, wherein the host cell is a prokaryotic host cell.

Claim 114 (original): The method according to claim 112, wherein the host cell is a mammalian cell.

Claim 115 (canceled)

Claim 116 (previously presented): The method according to claim 104, wherein the variable domain is a heavy chain variable domain and the HVR1 amino acid sequence is GYTFTNYGIN (SEQ ID NO: 14) or GYDFTHYGMN (SEQ ID NO:18).

Claim 117 (previously presented): The method according to claim 104, wherein the framework region is selected from the group consisting of FR1, FR2, FR3, and a mixture thereof.

Claim 118 (previously presented): The method according to claim 117, wherein the human subgroup FR consensus sequence is a heavy chain FR1 sequence with a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3.

Claim 119 (currently amended): The method according to claim 104, wherein the yield of the antibody or antigen binding fragment thereof with the ~~modified~~ substituted FR is improved at least 2 fold compared to the corresponding ~~unmodified~~ unsubstituted antibody or antigen binding fragment thereof.

Claim 120 (currently amended): The method according to claim 119, wherein the yield of the antibody or antigen binding fragment thereof with the ~~modified~~ substituted FR is improved at least 2 fold to 16 fold compared to the corresponding ~~unmodified~~ unsubstituted antibody or antigen binding fragment thereof.

Claim 121 (currently amended): The method of claim 104, wherein at least two ~~but not all~~ of the identified amino acid positions in at least one FR of the non-human antibody or antigen binding fragment thereof are: (i) substituted with amino acids in the corresponding position of the selected human subgroup consensus sequence, or (ii) deleted.

Claim 122 (currently amended): The method of claim 121, wherein the non-human antibody or antigen binding fragment thereof is an anti-vascular endothelial growth factor (VEGF) ~~a VEGF~~ antibody or antigen binding fragment thereof that comprises a heavy chain variable domain FR1 comprising the amino acid sequence of SEQ ID NO:3, and the FR is a heavy chain FR1 and one of the identified amino acid positions is position 6 or position 23 or both, and the other position is selected from the group consisting of position 1, 11, 13, 18, 19, and a mixture thereof.

Claim 123 (original): The method of claim 122 wherein amino acid positions 6 and 23 are substituted.

Claim 124 (original): The method of claim 122, wherein all of the amino acid positions at position, 1, 6, 11, 13, 18, 19, and 23 of the heavy chain FR1 are substituted.

Claim 125 (currently amended): The method of claim 104, wherein at least three ~~but not all~~ of the identified amino acid positions in a FR are: (i) substituted with the amino acid in the corresponding position in the selected human subgroup consensus sequence, or (ii) deleted.

Claim 126 (previously presented): The method of claim 125, wherein the FR is a FR1, a FR2, or a FR3.

Claim 127 (currently amended): The method of claim 104, wherein at least four ~~but not all~~ of the identified amino acid positions in all FR are: (i) substituted with the amino acid in the corresponding position in the selected subgroup consensus sequence, or (ii) deleted.

Claim 128 (canceled)

Claim 129 (currently amended): The method of claim 104 further comprising:

(a) comparing a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) amino acid sequence of a light chain variable domain of a non-human antibody or antigen binding fragment thereof to a corresponding HVR1 and/or HVR2 amino acid sequence of a human subgroup light chain variable domain consensus sequence and selecting the human subgroup light chain variable domain consensus sequence that has the most sequence identity with the HVR1 and/or HVR2 sequence of the non-human light chain variable domain;

(b) identifying at least one amino acid position in at least one FR in the non-human light chain variable domain selected from the group consisting of a FR1, a FR2, a FR3, a FR4 and a mixture thereof, wherein the amino acid position has a different amino acid than the amino acid at a corresponding position of the selected human subgroup light chain variable domain consensus sequence; and

(c) (i) substituting ~~modifying~~ the at least one ~~but not all~~ of the non-human amino acid positions identified in step (b) with the amino acid in the corresponding position of the selected human subgroup light chain variable domain consensus sequence to form a ~~modified~~ substituted light chain variable domain with a ~~modified~~ substituted FR, or (ii) deleting the at least one ~~but not all~~ of the non-human amino acid positions identified in step (b).

Claim 130 (currently amended): A method for improving the yield of a recombinant non-human antibody or antigen-binding fragment thereof in a host cell or cell culture, comprising:

(a) identifying at least one amino acid position in a heavy chain variable domain of the non-human antibody or antigen binding fragment thereof that is proximal to a cysteine (cys) residue that participates in an intrachain disulfide bond in the heavy chain variable domain;

(b) aligning a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) of the non-human heavy chain variable domain of step a) to corresponding HVR1 and/or HVR2 sequences of human subgroup heavy chain variable domain consensus sequences;

(c) selecting the human subgroup heavy chain variable domain consensus sequence having the most identity with the HVR1 and/or HVR2 amino acid sequence of the non-human heavy chain variable domain;

(d) substituting ~~modifying~~ at least one ~~but not all~~ of the amino acid positions in the non-human heavy chain variable domain an amino acid found at the corresponding position in the selected human subgroup heavy chain variable domain consensus sequence to form a ~~modified~~ substituted non-human heavy chain variable domain; and

(e) expressing the recombinant antibody or antigen binding antibody fragment thereof comprising the ~~modified~~ substituted non-human heavy chain variable domain, wherein the ~~modified~~ substituted non-human antibody or antigen binding antibody fragment thereof has improved folding efficiency and yield in the host cell or cell culture as compared to the folding efficiency and yield of a corresponding ~~unmodified~~ unsubstituted antibody or antigen binding antibody fragment.

Claim 131 (previously presented): The method of claim 1, wherein the host cell is a prokaryotic cell or a eukaryotic cell.

Claim 132 (previously presented): The method of claim 131, wherein the host cell is a filamentous fungi or yeast cell, an insect cell, a mammalian cell or a bacterial cell.

Claim 133 (previously presented): The method of claim 132, wherein the host cell is an *Archaebacteria* or a *Eubacteria*, or a Gram-negative or a Gram-positive organism.